REMARKS

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Utility rejection under 35 U.S.C. § 101

Claims 3-7, 9, 10, 12, 13, 46, and 57-59 were rejected under 35 U.S.C. § 101, based on the allegation that the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility (Office Action, September 5, 2003; page 3). This rejection is traversed.

The Office Action asserts that "[t]he essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility" (Office Action, September 5, 2003; page 3), and that the utility of the claimed polynucleotide as a control in toxicology testing "is speculative at best, as well as not being specific or substantial in that any polynucleotide may possess the property of being a marker for some toxic response" (Office Action, September 5, 2003; page 7). The Office Action dismisses the references which demonstrate that the asserted utilities were well-known at the time the application was filed, and that the asserted utilities are specific, substantial, and credible, by stating that "the references of Rockett et al, Lashkari et al., Nuwaysir et al., Bork and Steiner et al. do not exemplify the state of the art at the time of the instant invention because they were published 2-3 years after the filing date of the instant application and they rely on information that was not available at the time of the instant invention" (Office Action, September 5, 2003; page 9). However, the Office Action has presented no evidence that the information relied on was not available at the time of the instant invention. Moreover, the Office Action dismisses the objective evidence of the Bedilion Declaration by stating that "it merely presents Applicants' arguments in declaratory form, such arguments having already been answered o the record" (Office Action, September 5, 2003; page 10). The Office Action is incorrect. The Bedilion Declaration is not a mere restatement of the Applicants' arguments; this Declaration is objective evidence of the state of the art at the time the application was filed.

To further address the Office Action's arguments, Applicants herewith submit three additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments. These Declarations are the Declaration of John C. Rockett (the "Rockett Declaration"), the Declaration of Vishwanath R. Iyer (the "Iyer Declaration"), and a further Declaration of Tod Bedilion (hereinafter the "Second Bedilion Declaration"). In addition, Applicants herewith submit two (2) references that were published in the month following the priority date of the instant application. The original Bedilion Declaration, the Rockett Declaration, the Iyer Declaration, the Second Bedilion Declaration, the references of record, and the two (2) references submitted herewith fully establish that, prior to the July 15, 1996 filing date of the Coleman '655 application (from which the instant application claims priority), it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;
>
> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in published PCT applications WO 95/21944 (Reference No. 1) and WO 95/20681 (Reference No. 2).

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function. . . . [abstract]

The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof. [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . . [or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 - 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]

Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative gene transcript analysis"), filed in 1994 by Applicants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Patent No. 5,840,484, issued November 24, 1998; U.S. Patent No. 6,114,114, issued September 5, 2000; and U.S. Patent No. 6,303,297, issued October 16, 2001. The specification describes the use of trascript expression *patterns*, or "images," each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> The invention provides a "method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens." [abstract]
>
> [W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood. [page 2]
>
> The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts. [page 6]
>
> High resolution analysis of gene expression be used directly as a diagnostic profile. . . . [page 7]

The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed. [page 7]

The invention . . . includes a method of comparing specimens containing gene transcripts. [page 7]

The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens. [page 8] [i.e., the results yield data analogous to microarrays]

Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made. [page 8]

In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities. [page 9]

In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens . . . [page 9]

[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. [pages 9-10]

The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as 'gene transcript image analysis' or 'gene transcript frequency analysis.' The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism. [page 11]

The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few. [page 12]

[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy

patients. The patient has the disease(s) with which the patient's data set most closely correlates. [page 12]

For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues . . . [page 12]

In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology . . . [page 12]

In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond. [page 12]

In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models. [page 14]

In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition. [page 14]

An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined. [page 15]

[T]his research tool provides a way to get new drugs to the public faster and more economically. [page 36]

In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker. [page 38]

[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients. [page 39]

In light of this and other evidence of the state of the art, one of ordinary skill in the toxicology arts would conclude that "[i]t is my opinion,[1] therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology." (Rockett Declaration, ¶ 18).

In the Second Bedilion Declaration, Dr. Bedilion explains why a person of skill in the art in 1995 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Second Bedilion Declaration, e.g., at ¶¶ 4-7). In the Iyer Declaration, Dr. Iyer explains why a person of skill in the art in 1995 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include -- and as a biologist I would want my microarray to include -- each newly identified gene as a probe." (Iyer Declaration, ¶ 9).

Furthermore, in the Rockett Declaration, Dr. Rockett explains that "there are a number of other differential expression analysis technologies that precede the development of microarrays, some by decades, and that have been applied to drug metabolism and toxicology research, including: (1) differential screening; (2) subtractive hybridization, including variants such as chemical cross-linking subtraction, suppression-PCR subtractive hybridization and representational difference analysis; (3) differential display; (4) restriction endonuclease facilitated analyses, including serial analysis of gene expression (SAGE) and gene expression fingerprinting and (5) EST analysis." (Rockett Declaration, ¶ 7).

---

[1]"Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

The Office Action alleges that the use of the claimed polynucleotide in toxicology testing "would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO:2. Because of this, such a utility is not specific and does not constitute a 'well-established' utility" (Office Action, September 5, 2003; pages 3-4).

Applicants' submission of additional facts overcomes this concern. Those facts demonstrate that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Applicants' claimed polynucleotides as gene-specific probes ***depends upon*** specific properties of the polynucleotides, that is, their nucleic acid sequences.

"[E]ach probe on . . . [a 'high density spotted microarray[]'], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, ***binds specifically*** and with minimal cross-hybridization, to the probe's cognate transcript" (Rockett Declaration, ¶ 10(i); emphasis added); "[e]ach gene included as a probe on a microarray provides ***a signal that is specific to the cognate transcript***, at least to a first approximation" (Iyer Declaration, ¶ 7; emphasis added; see the footnote at ¶ 7 for a slightly more "nuanced" view). Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene expression profiling" (Rockett Declaration, ¶ 10(ii)); equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectably by the device, increasing the resolving power of the device" (Iyer Declaration, ¶ 7).

Although not required for the present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biology techniques developed over the past 30-40 years.

For at least the above reasons, the reasons presented in the Response to Office Action of June 18, 2003, and the objective evidence of the original Bedilion Declaration, the Second Bedilion Declaration, the Iyer Declaration, and the Rockett Declaration, withdrawal of this rejection under 35 U.S.C. § 101 is requested.

II. Utility/enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 3-7, 9, 10, 12, 13, 46, and 57-59 were rejected under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility under 35 U.S.C. § 101.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

III. Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 3, 6, 7, 9, 12, 13, 46, and 59 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. This rejection is traversed.

The Office Action asserts that the "specification and claims do not indicate what are the distinguishing attributes shared by the members of the genus for which the common portion is responsible for functional activity" (Office Action, September 5, 2003; page 11 and again on page 13). The Office Action's position is contrary to the Patent and Trademark Office's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. [footnotes omitted]

Here, there simply is no requirement that the specification or claims indicate distinguishing attributes responsible for functional activity because the claims already provide sufficient structural

definition of the claimed subject matter. That is, the claimed variants and fragments are defined in terms of SEQ ID NO:1 and SEQ ID NO:2. Because the claimed variants and fragments are defined in terms of SEQ ID NO:1 and SEQ ID NO:2, the precise chemical structure of every variant and fragment within the scope of the claims can be discerned. The Patent Office's position is nothing more than an attempt to require Applicants to unduly limit the scope of their claimed invention.

The Office Action specifically alleges that "Applicants have not provided a written description for 'a polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1' as recited for example in claim 3" (Office Action, September 5, 2003; page 11). To the contrary, the specification specifically provides for such polynucleotides. For example, the specification states that:

> Included within the scope of the present invention are alleles of MCPP. As used herein, an 'allele' or 'allelic sequence' is an **alternative form** of MCPP. Alleles result from a mutation, ie, a change in the nucleic acid sequence, and generally produce altered mRNAs or polypeptides whose structure or function **may or may not be altered**. (Specification at page 8, lines 4-8; emphasis added)

Furthermore, the specification explicitly provides examples of alternative forms of MCPP. For example, the specification states that:

> The present invention also encompasses MCPP variants. A preferred MCPP variant is one having at least 80% amino acid sequence similarity to the MCPP of SEQ ID NO:1, a more preferred MCPP variant is one having at least 90% sequence similarity to SEQ ID NO:1, and a most preferred MCPP variant is one having at least 95% sequence similarity to SEQ ID NO:1. (Specification at page 4, lines 17-21)

Thus, the specification provides an adequate written description of the claimed polynucleotides encoding the recited polypeptide variants.

The Office Action asserts that the genus of recited polynucleotide fragments is highly variant because "a significant number of structural differences between genus members is permitted" (Office Action, September 5, 2003; page 13). To the contrary. The genus of recited polynucleotide fragments is not highly variant because the members of the genus are defined within the structural framework of

the polynucleotide sequence of SEQ ID NO:2, or of the recited naturally occurring variants of SEQ ID NO:2.

The Patent Office Guidelines indicate that evidence that Applicants were in possession of the claimed invention can include "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or** some combination of such characteristics" (P.T.O. Guidelines, *supra*; emphasis added). The claimed polynucleotides have been described by chemical structure (e.g., relation of the recited polynucleotides to SEQ ID NO:2, relation of the recited polypeptides to SEQ ID NO:1), physical properties (e.g., occurrence in nature of the recited variant sequences), and chemical properties (e.g., immunogenic activity or chemotactic activity of the recited fragments). Therefore, the written description requirement has been met.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be withdrawn.

IV. Enablement rejections under 35 U.S.C. § 112, first paragraph

Claims 3, 6, 7, 9, 12, 13, and 46 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to use the claimed variants and fragments. This rejection is traversed.

With respect to the claimed variants, the Office Action asserts that "Applicants disclose that variants of MCPP include deletions, substitutions or additions of amino acids without abolishing activity. Therefore, the claimed genus of polynucleotides encoding MCPP polypeptides encompasses variants that share activity, however, the specification does not teach how to make a polynucleotide sequence encoding a polypeptide having an amino acid sequence less than SEQ ID NO:1, that would share those activities" (Office Action, September 5, 2003; page 14). To the contrary. A skilled artisan would understand, from the specification and the state of the art at the time the application was filed, how to

make and use variants sharing the activity of MCPP, without undue experimentation. For example, a skilled artisan could use the assays disclosed in Example IX at page 37 of the specification to obtain variants sharing the chemotactic activity of MCPP. Furthermore, the claimed variants include polynucleotides encoding polypeptides "whose structure or function **may or may not be altered**" (Specification, e.g., at page 8, lines 4-8). Since the specification enables all of the recited variants, whether or not they share the activity of MCPP, it is not necessary to separately and additionally enable those variants which share the activity of MCPP.

Furthermore, the Office Action asserts that "Applicants are not claiming polynucleotide sequences that are 'probes' but polynucleotide sequences that encode MCPP proteins" (Office Action, September 5, 2003; page 14). The Office Action is incorrect. Polynucleotide sequences that encode MCPP proteins can nevertheless be used as "probes." The claimed polynucleotides are enabled as long as a skilled artisan could make and use the claimed polynucleotides, without undue experimentation. Since a skilled artisan could use the claimed polynucleotides as "probes," the claimed polynucleotides are enabled, regardless of whether a skilled artisan could additionally use them based on their encoding MCPP polypeptides.

With respect to the claimed fragments, the Office Action asserts that "the recitation of 'at least 60 contiguous nucleotides . . .' in claim 13, is not a sufficient structural limitation . . . [b]ecause of the presence of the term 'comprising' in claim 13" (Office Action, September 5, 2003; pages 14-15). Such, however, is not the case.

The Office Action's assertions seem to imply that the use of the transitional phrase "comprising" in the claims requires that the specification provide enablement for any possible element which could be a part of, but is not essential to, the claimed subject matter. However, the transitional phrase " '[c]omprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." M.P.E.P. § 2111.03 (citing *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997)).

The specification has provided enablement for polynucleotides comprising at least 60 contiguous nucleotides of SEQ ID NO:2, or comprising at least 60 contiguous nucleotides of variants of SEQ ID NO:2. For example, the specification provides enablement for the recited polynucleotide fragments as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:2 (Specification, e.g., at page 6, line 35 to page 7, line 17; page 15, line 26 to page 16, line 1; page 21, line 36 to page 22, line 21; and Example VI at page 36). One of skill in the art would understand how to make and use polynucleotides "comprising" at least 60 contiguous nucleotides of SEQ ID NO:2, or comprising at least 60 contiguous nucleotides of variants of SEQ ID NO:2, without an explicit disclosure of every possible element which could be a part of, but is not essential to, the claimed subject matter.

Furthermore, the Office Action asserts that "[e]ven if Applicants recited a functional limitation for the MCPP polypeptide in the instant claims . . . [t]he instant specification does not teach which polynucleotides encoding polypeptides would predictably be associated with that function" (Office Action, September 5, 2003; page 15). However, it is not necessary for a polynucleotide fragment to encode a polypeptide fragment which shares the activity of the SEQ ID NO:1 polypeptide in order for one of skill in the art to be able to use that polynucleotide fragment without undue experimentation. One of skill in the art could make and use the claimed polynucleotide fragments without undue experimentation, based on the specification and the state of the art at the time the application was filed. For example, one of skill in the art would know how to use the claimed polynucleotide fragments as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:2 (Specification, e.g., at page 6, line 35 to page 7, line 17; page 15, line 26 to page 16, line 1; page 21, line 36 to page 22, line 21; and Example VI at page 36). Since a skilled artisan would know how to make the claimed polynucleotide fragments, and use them as hybridization probes and/or PCR probes, the Office Action's assertion that "[t]here is no guidance in the specification for how to make and use polynucleotides encoding proteins having the amino acid sequences anything less than that disclosed in SEQ ID NO:1" (Office Action, September 5, 2003; page 15) is incorrect.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotide variants and fragments. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited polynucleotide variants and fragments.

For at least the above reasons, withdrawal of these rejections is requested.

V. Rejection of claim 3 under 35 U.S.C. § 112, second paragraph

Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the recitation of the phrase "chemotactic activity" is indefinite. The Office Action asserts that "it is unclear for which type of cells the polypeptide encoded by the claimed polynucleotide, is chemotactic" (Office Action, September 5, 2003; page 17). This rejection is traversed.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also M.P.E.P. § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of

what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir.1983). The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph.

Claim 3 recites polynucleotides which encode polypeptide fragments which have chemotactic activity. The specification provides methods to measure chemotactic activity at, for example, page 37, lines 17-33. The specification also provides examples of cell types which can be assayed using the disclosed method:

> Specificity of the chemoattraction is determined by performing the assay on fractionated populations of cells such as enriched populations of **neutrophils, mononuclear cells, monocytes or lymphocytes** obtained by density gradient centrifugation. Specific **T cell** populations can be purified using CD8+ and CD4+ specific antibodies for negative selection. (Specification, page 37, lines 29-33; emphasis added)

Furthermore, the specification states that CC chemokines can have chemotactic activity for "specific cell types such as monocytes, macrophages, basophils, eosinophils, T lymphocyte, and fibroblasts" (e.g., at page 1, lines 28-31). Thus, a skilled artisan would reasonably understand that the recited polypeptide fragments have chemotactic activity for one or more specific cell types, and would also know what types of cells the recited fragments could have chemotactic activity for.

For at least the above reasons, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

VI. Rejection of claims 3, 12, and 13 under 35 U.S.C. § 112, second paragraph

Claims 3, 12, and 13 were rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the recitation of "naturally occurring" is indefinite. The Office Action asserts that "[i]t is unclear whether this term imposes a required limitation on the claim, such that it only encompasses, for example, polynucleotides amplified from human cDNA, or only sequences produced by digestion with restriction enzymes of DNA isolated from tissue which contains polynucleotides encoding the polypeptide, or if the claim encompasses all polynucleotide sequences that encode the polypeptide" (Office Action, September 5, 2003; page 17). This rejection is traversed.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also M.P.E.P. § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir.1983). The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph.

The term "naturally occurring" is not a limitation of the claimed polynucleotides themselves, as the Office Action seems to imply. This term is a limitation of the **polynucleotide sequences** comprised by the claimed polynucleotides and of the **amino acid sequences** comprised by the recited polypeptides encoded by the claimed polynucleotides. For example, the "variant" language of claim 3 recites an isolated polynucleotide encoding "a polypeptide comprising a **naturally occurring amino acid sequence**." Similarly, the "variant" language of claim 12 recites an isolated polynucleotide "comprising a **naturally occurring polynucleotide sequence**." The term "naturally occurring," in the context of polynucleotide and amino acid sequences, is supported in the specification at, for example, page 4, lines 2-7 and 14-16; page 8, lines 4-13; page 10, lines 27-29; and page 26, lines 26-34. One of skill in the art would reasonably understand that the recitation of "naturally occurring" sequences encompasses any sequence which occurs in nature.

Furthermore, one of skill in the art would reasonably understand, based on the language of the claims, that the claimed isolated polynucleotides are not naturally occurring; they are actual physical molecules which can be made by man. For example, the claimed isolated polynucleotides could be isolated from a natural source, they could be amplified by PCR from a natural source, they could be produced by recombinant DNA techniques, or they could be chemically synthesized *de novo*. The chemical structures of these man-made polynucleotides are based on the information provided by the

naturally occurring amino acid sequence of SEQ ID NO:1, and the naturally occurring polynucleotide sequence of SEQ ID NO:2. Therefore, the claims are definite in their recitation of isolated, man-made polynucleotides which have sequences derived from naturally occurring molecules.

For at least the above reasons, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

VII. Rejection of claim 58 under 35 U.S.C. § 112, second paragraph

Claim 58 was rejected under 35 U.S.C. § 112, second paragraph, because it recites "a polynucleotide comprising the amino acid sequence of SEQ ID NO:2" (Office Action, September 5, 2003; page 17). This rejection is traversed.

Nevertheless, to expedite prosecution, claim 58 has been amended to recite "a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2," as suggested by the Examiner. Therefore, withdrawal of this rejection is requested.

VIII. Rejection of claims 6, 7, 9, 46, and 59 under 35 U.S.C. § 112, second paragraph

Claims 6, 7, 9, 46, and 59 were rejected under 35 U.S.C. § 112, second paragraph, because they are allegedly "dependent on the above rejected claims for their limitations" (Office Action, September 5, 2003; page 17). This rejection is traversed.

With respect to claims 6, 7, 9, and 46, Applicants believe that the base claims particularly point out and distinctly claim the subject matter of the invention (See, e.g., §§ V and VI). Therefore, withdrawal of this rejection of claims 6, 7, 9, and 46 is requested.

With respect to this rejection, claim 59 is directed to inventions defined by SEQ ID NO:2. The Office Action's rejection is based on the alleged indefiniteness of claims drawn to claims reciting the phrase "chemotactic activity" and claims reciting the term "naturally occurring." Thus, this rejection should not apply to claim 59. For at least this reason, this rejection of claim 59 should be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

Respectfully submitted,

INCYTE CORPORATION

Date: December 5, 2003

Terence P. Lo, Ph.D.
Limited Recognition (37 C.F.R. § 10.9(b)) attached
Direct Dial Telephone: (650) 621-8581

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886